
محاضره سلاحف
النينجا
دكتور مايكل
انجلو

easy

Opioids are often used in acute care :

- After the trauma resulting in **spinal cord injury (**SCI), **strong opioids (**such as **morphine)** are possibly used, and would have been very good at controlling the acute pain of the injury.

- **Over time however**, this situation changes and opioids become less and less effective. **For chronic pain, opioids are NOT very effective at all**, and they often have very **severe and unpleasant side effects**

Mechanism of action:

Opioid drugs produce their action by acting on opioid receptors:

- **Opioid receptors are membrane receptors coupled to G-protein:**

1- ⊗ Adenylate cyclase → ⊗ cAMP.

2- Open K^+-Channel → Hyperpolarization.

3- Block Ca^{2+}-Channel

- **Types of opiod receptors and action results of their activation:**

1- **Mu** (μ_1 & μ_2): Analgesia (Spinal & Supra-spinal), Euphoria, Sedation, Dependence, ↓ R.C., Miosis & Constipation.

2- **Kappa** (κ_1, κ_2 & κ_3)**:** Analgesia (Spinal & Supra-spinal), Dysphoria, Psychotomimetic, Less ↓ R.C. & Less Miosis

3- **Delta** (δ_1 & δ_2)**:** Analgesia (Spinal mainly) & Constipation.

It is to be noted that :

- There are a range of medications that can be helpful for spinal cord injury pain after the acute phase :
- It is very important to match the type of medication to the type of pain for the best results:

➢ Musculoskeletal pain:

responds well to simple analgesics (paracetamol, NSAIDs)

➢ Neuropathic pain :

Some of the anti-convulsants (or anti-epileptics) are used like gabapentin and pre-gabalin and they work by reducing the excitability and the abnormal firing in

Contraindications of Morphine:

- ***1- Head injury:***
  - ***a- Miosis → Interfere with proper diagnosis.***
  - ***b- Morphine ⇩ R.C. → ⇧ CO_2 → Cerebral V.D. → ⇧ Synthesis of C.S.F. → ⇧ Intra-cranial tension → More ⇩ R.C.***
- 2- ⇧ Intra-cranial tension.
- 3- Epilepsy.
- 4- Respiratory diseases e.g. Asthma & C.O.P.D.
- 5- Acute abdomen → Morphine → Analgesia → Interfere with proper diagnosis.
- ***6- Pregnancy & Labor:***
  - ***a- Pregnancy → Addict fetus → Withdrawal symptoms after labor.***
  - ***b- Labor → Neonatal asphyxia***.
- 7- Liver disease → Deficient metabolism.
- 8- Extremities of age → Deficient metabolism.

Advantages of combination of carbidopa with levodopa:

1. Lowers the daily dose of levodopa by four- to fivefold
2. Decreases the severity of the peripheral side effects
3. Increases the central effect

I) Dopaminergic drugs

Most effecti ve

1) Levo dopa/ Carbidopa

Main stay of therapy

Mechanism of action:

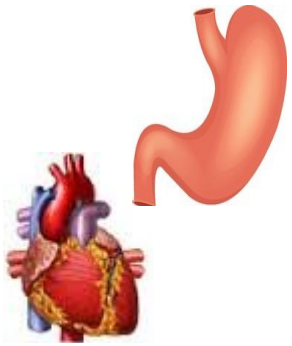
Levo dopa

- An immediate **precursor of DA** which **crosses BBB** (DA can not) converted **centrally** via **Dopa Decarboxylase (DD)** enzyme into **DA**.

Carbidopa

- Without *carbidopa*, much of levodopa is decarboxylated to DA in the periphery, resulting in peripheral adverse effects.
- **Carbidopa**, a **peripheral Dopa Decarboxylase enzyme** inhibitor → ↓ levodopa metabolism peripherally → ↑ its availability centrally.

Adverse effects of levodopa:

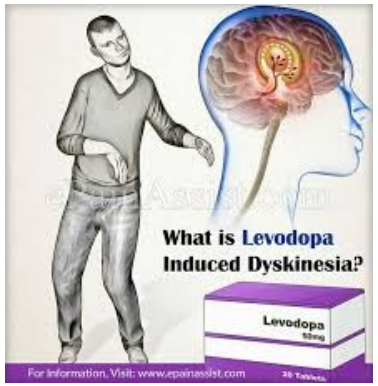


A) Peripheral (↓ with carbidopa)

- GIT: Anorexia, nausea, and vomiting (CTZ stimulation), ▯ HCl
- CVS: postural hypotension and arrhythmias (C.I in ISHD)

B) Central (↑ with carbidopa)

- Confusion, Hallucinations, psychosis (especially in the elderly)
- Abnormal involuntary movements (dyskinesias) (↑DA in basal ganglia)



C) Fluctuations in response

- End of dose akinesia
- On-off effect

Fentanyl (Synthetic)

- 1- Derivative of *Meperidine*.
- 2- **Strong** μ-Agonist → **Strong** Analgesic → **80** Times > Morphine
- 3- *High Lipid solubility*: I.V. → Rapid Onset + Short duration (Redistribution)
- 4- Used as *I.V. Anesthesia*:
  - a- Fentanyl alone, *But* → Vomiting.
  - b- Fentanyl + Droperidol (Major tranquillizer) → *Neurolept- Analgesia*
  - c- Fentanyl + Droperidol + Nitrous oxide → *Neurolept-Anesthesia*
  - *NB) The emetic effect of Fentanyl is # Anti-emetic effect of Droperidol.*
- 5- *Adverse Effects* → Vomiting, Marked RC & Muscle tone → Trunkal rigidity

N.B.: Droperidol is a dopamine antagonist: blocks dopamine receptors in the CTZ, TTT of nausea & vomiting

mcq

Acute Morphine Poisoning:

- a- *Manifestations*: Coma + PPP + Hypoventilation, Hypoxia, Hypotension & Hypothermia.
- b- *Cause Of Death* → Respiratory Failure.
- c- *Treatment*:
  - Artificial respiration. No pure O_2 → Apnea.
  - Stomach wash in *Every* case even after parenteral poisoning.
    Use K-Permanganate + Charcoal + $MgSO_4$.
  - Specific Morphine Antagonists e.g. ***Naloxone*** (0.4 mg I.V.).

Dantrolene cont.

Dantrolene uses:

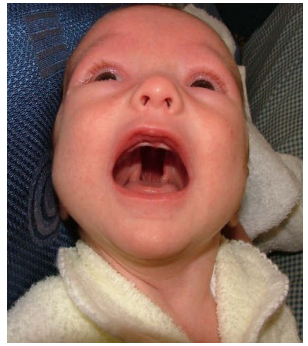
Dantrolene has demonstrated efficacy for spasticity in:

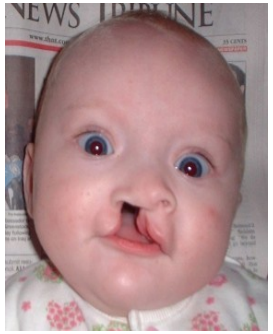
- Spinal cord injury, cerebral palsy, and multiple sclerosis.
- Brain injury.
- The drug of choice for the prevention and ***treatment of malignant hyperthermia***, (a life-threatening genetic disorder triggered by volatile anesthetics and the depolarizing neuromuscular blocking agent succinylcholine)

Phenytoin side effects (8H)

P alate H e N +2M

- **Dose related side effects:** Nystagmus, diplopia, ataxia, sedation and drowsiness
- **Non dose related:**
  - Gingival **H**yperplasia (gum hypertrophy), **H**irsutism, acne, rash, **H**epatotoxicity and coarsening of features
- **Chronic use:** decrease bone mineral denisty (vit D metabolism leading to **H**ypocalcemia), megaloblastic anemia, **H**yperglycemia, Neuropathy
- **H**ypersensitivity: rash, IV infusion side effects: phlebitis and hypotension
- Pregnancy category D



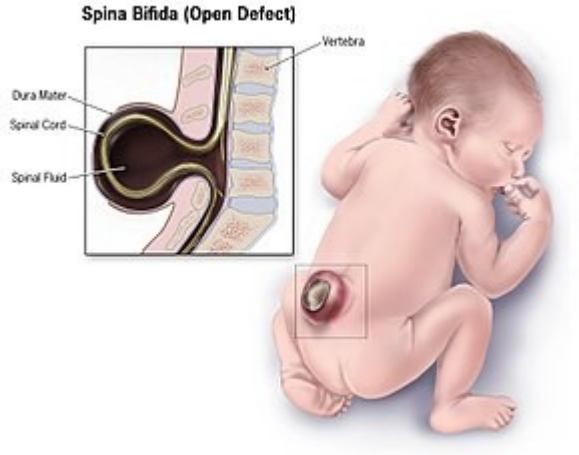


fetal hydantoin syndrome

- **Cleft lip and palate**
- **Congenital Heart disease**
- **Hypoplasia**
- **Slowing of growth**
- **Mental deficiency**

Valproate side effects

- Most common nausea, vomiting and mild drowsiness
- Fatal Hepatotoxicity
- Fatal pancreatitis
- Hematological: Thrombocytopena
- Suicidal thoughts
- Severe birth defect (spina bifida, and lower IQ)



Ethosuxamide

- block t type ca channel
- Uses in ***absence seizures***
- Side effects:
  - gastric distress, nausea and vomiting
  - Pregnancy category C
  - It ***may increase frequency of grand mal seizures*** in some patients

Adverse effects

1) MAOIs + tyramine:

- Individuals receiving a MAOI are **unable to degrade tyramine obtained from the diet**.
- **Tyramine** causes the release of large amounts of stored catecholamines from nerve terminals, resulting in **a hypertensive crisis**
- Patients **must avoid** tyramine-containing foods.
  - **Tyramine** is contained **in foods**, such as **aged cheeses** and **meats**, **chicken liver**, **smoked fish**, and **red wines**.
- **Management of tyramine-induced hypertension**

  By: Phentolamine or prazosin

SSRIs - Pharmacokinetics

- **Fluoxetine:**

  - has a much longer half-life (50 hours)

  sustained release preparation (once-weekly)

  - its metabolite S- norfluoxetine is as potent as the

  parent compound & its half-life is ~ 10 days.

- **Fluoxetine and Paroxetine**

  Potent inhibitors of a hepatic cytochrome P450

  isoenzyme (CYP2D6) responsible for the elimination

Chlorpromazine

- Explain the adverse effects of chlorpromazine

1- C.N.S. Side Effects

- Drowsiness & *Sedation(antihistaminic ef*
- Extrapyramidal Manifestations:

1- Dystonia (painful muscle spasm twistin
2- Akathisia (motor restlessness).
3- Parkinsonism(shuffling gait, masked face, M. rigidity)
4- Tardive dyskinesia(involuntary movement of orofascial

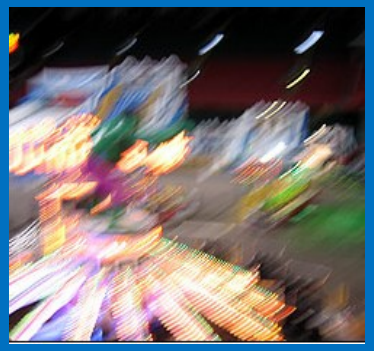
Muscles)

- Neurolept-malignant Syndrome:
  Idiosyncratic reaction (similar to malignant

Chlorpromazine Side Effects

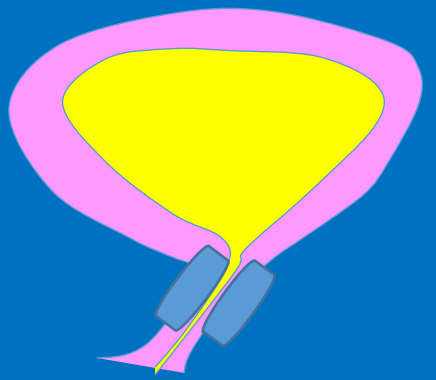
2. Atropine like Side Effects:

- Dry mouth



- Blurred vision & I.O.P

- Tachycardia



- Urine retention

B) Caffeine

1- With *E*rgotamine

Cafergot in acute attack of Migraine headache.

With Aspirin or paracetamol in simple headache.

NaturesPharm

2- Poisoning by C.N.S. depressants e.g. *H*ypnotics.

B) Caffiene:

Wide safety margin

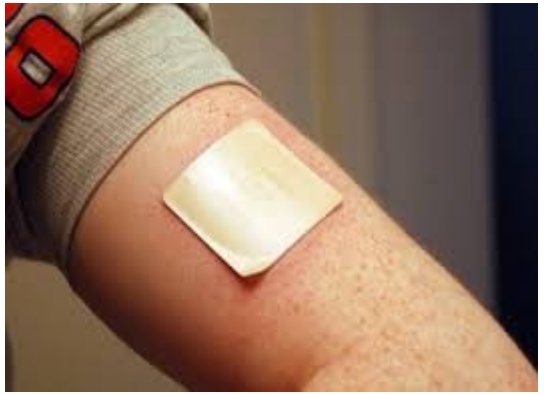
C.N.S insomnia, anxiety, and agitation, finally convulsions.

G.I.T. Hyperacidity and then emesis.

The **lethal dose** is 10 g of *caffeine* , which induces **cardiac arrhythmias.**

Death from *caffeine* is, therefore, **highly uncommon.**

Methylphenidate is available in extended-release oral formulations and as a transdermal patch for once-daily application.



pH and Local Anesthetic Activity

weak basic amine (Pka =7.9-9)

Two forms exist simultaneously

- non ionized form (cross membrane)
- ionized form (active form)

The relation between the two forms depends on

- PKa of the local anesthesia
- PH of the tissue

Extracellular & intracellular pH effect of Local anesthetic activity

- ***Extracellular pH:***
  - ↓pH (acidosis) ……m
    …….less penetration
  - ↑pH (alkalosis)……more non-ionized form……..more penetration (rapid onset)

- Repeated injection
- infection

- Add NaHCO3

- Intracellular pH:
  - ↓pH (acidosis) …… more ionized form
    …….more active

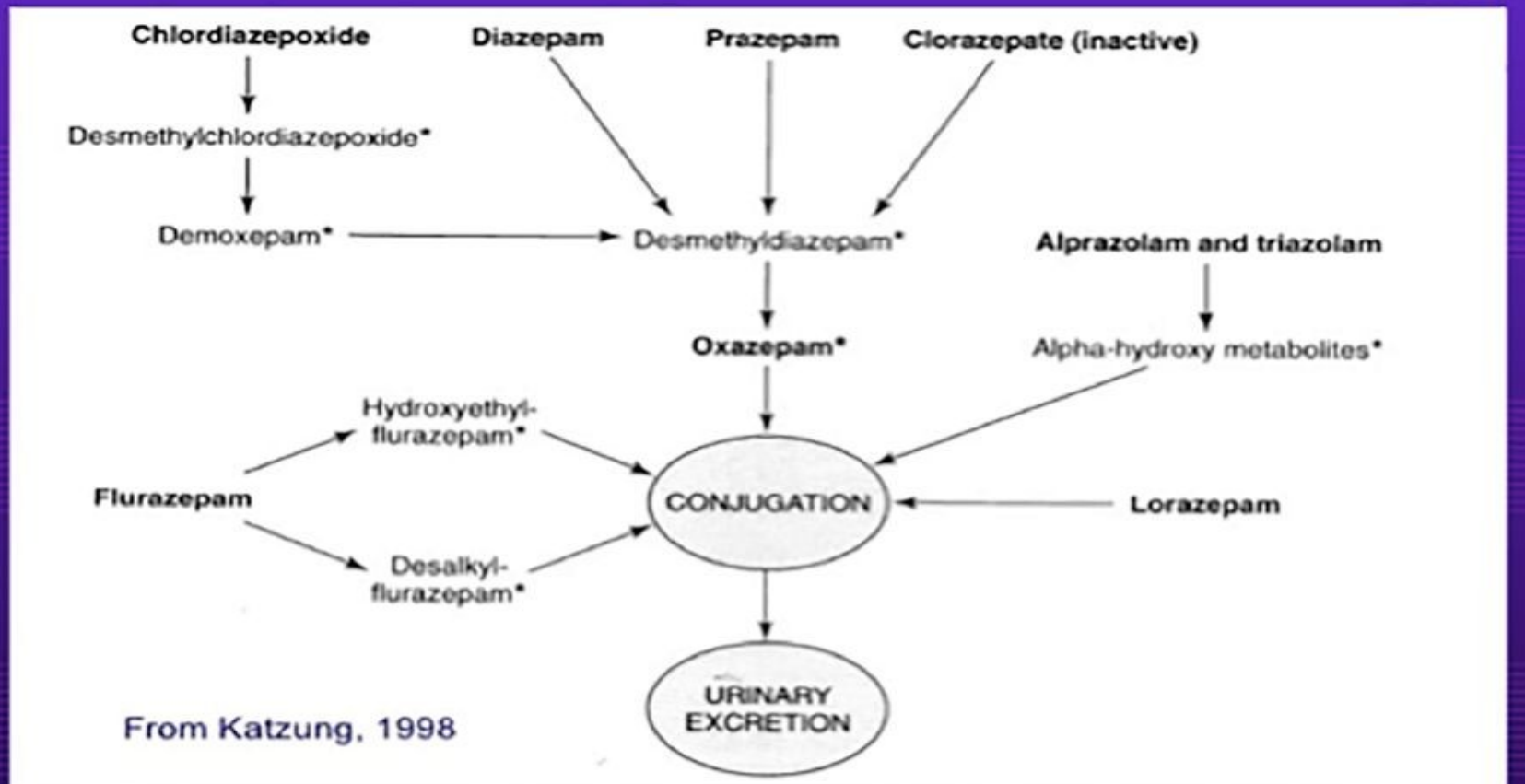
- Prepare carbonated solution

Influence of the adjuvant used

Vasoconstrictors are added to LA (except cocaine) to prolong duration of action and decrease systematic toxicity.

NB: LA except cocaine induce VD……
↑absorption…… ↑systemic toxicity&↓effect

- **Epinephrine is the commonly used one**
- **In contraindication of epinephrine, Felypressin (vasopressin analogue) is used.**
- **Vasoconstrictors are CI in anesthesia of fingers, toes & nose gangrene.**



LOT = *Lorazepam*, Oxazepam, temazepam used in *liver and renal dysfunction*.

-They have no active metabolites and no CYP metabolism only conjugation (conjugation is lately affected in severe liver cirrhosis.)

-Also better in renal dysfunction as they don't heve active metabolites which is urinary excreted

Advantages of Benzodiazepines over barbiturates

1- Wide safety margin

2- Has an antidot

3- No enzyme induction

4- No porphyria

5- Less tolerance and dependence (but more serious)

6- Less respiratory and CVS depression

Z- hypnotics (night calm)

Non BZD acting on BZ 1 receptors

Antagonized by flumazenil

Sedative hypnotics that are used in non anxiety induced insomnia

BZDs toxicity:

1- Prolonged sleep and coma

Same symptomatic treatment AS barbiturates

2- Flumazenil an antidot

Mechanism of action:

- *Aspirin* is a weak organic acid that **irreversibly acetylates** (and, thus, inactivates) **cyclooxygenase**
- The **other NSAIDs**, are all **reversible** inhibitors of cyclooxygenase.
- Aspirin (acetylsalicylic acid) blocks the cyclooxygenase pathway by **inhibiting COX1 and COX2 (non selective)**
- This results in ↓ **PGs, prostacyclin and thromboxane**.

b. **Antipyretic action:**

- Salicylates **lower body temperature** in patients with fever **by inhibiting PGE2 synthesis and release.**
- *Aspirin and other NSAIDs* ***reset*** **the "thermostat" in CNS** toward normal. This rapidly **lowers the body temperature** of febrile patients by increasing heat loss as a result of **peripheral vasodilation and sweating.**

Salicylates

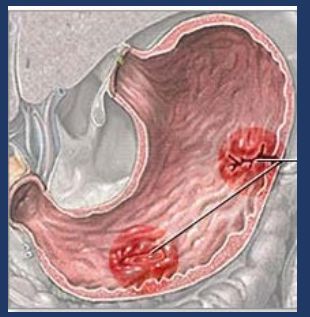
Drug Interactions:

- **Salicylates displaces other drugs from plasma proteins e.g:**

Oral anticoagulants
Oral hypoglycemics
Phenytoin & valporic acid

Side Effects

1- Gastric irritation:



Peptic ulcer

Bleeding

2- Bleeding Tendency (↓ platelet aggregation)

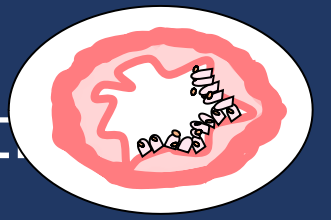
Asprin + warfar

3- *Small dose*

Nephropathy

4- Aspirin-induced asthma :

Bronchial asthma in predisposed pat



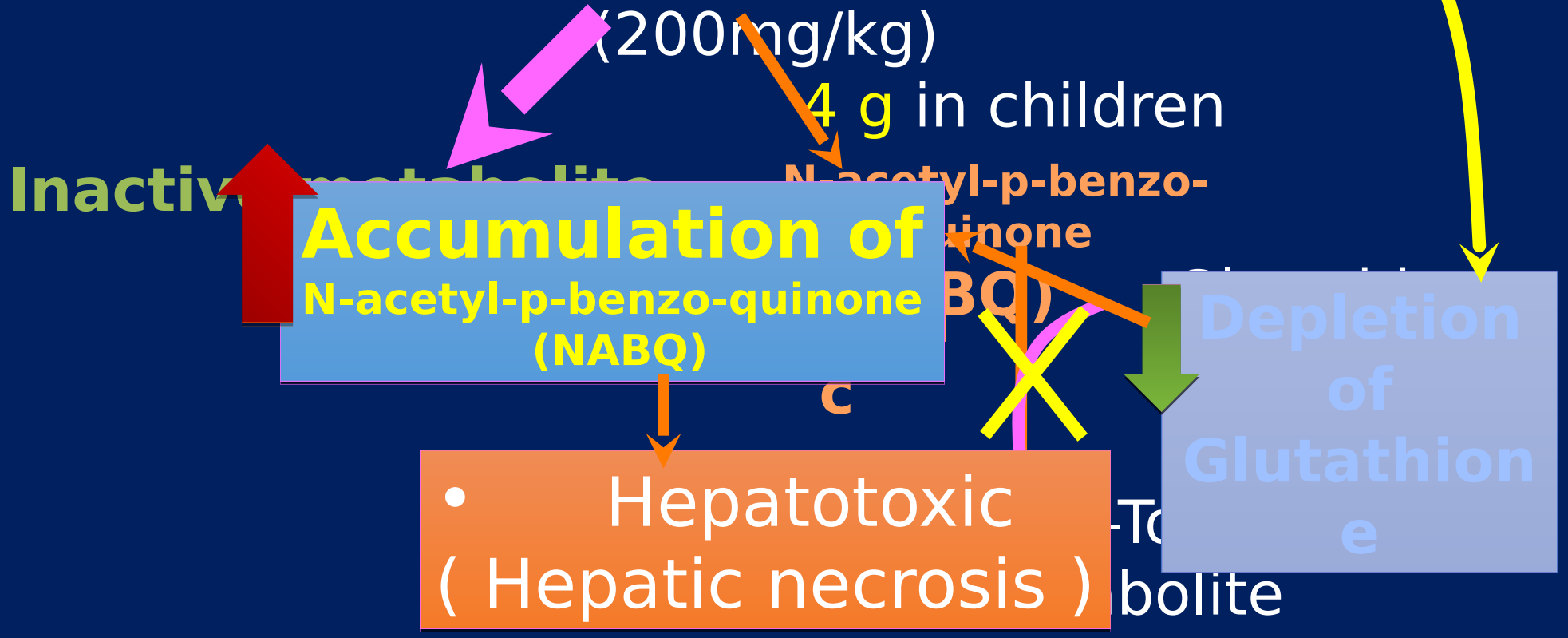
Acetaminophen Acute Toxicity:

Toxic dose = single dose of 10-15 g in adults

Paracetamol

(200mg/kg)

4 g in children

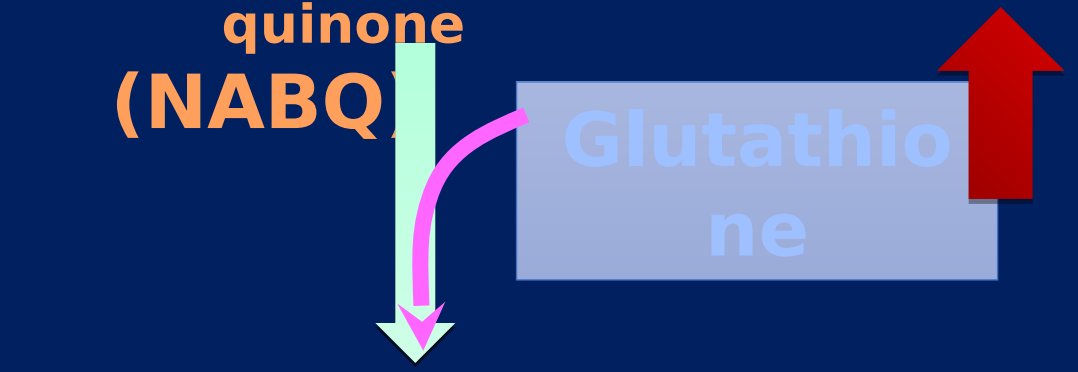


Acetaminophen Acute Toxicity:

Treatment

N-Acetylcysteine I.V
(Rich in S-H)

N-acetyl-p-benzo-quinone
(NABQ)



Non-Toxic metabolite

Drug therapy of migraine

Severe migraine < acute attack > when

These patients suffer 2- 3 or more attacks per month of severe throbbing headache lasting 12-4 8 hours, often accompanied by vertigo, vomiting and other symptoms; the subject is grossly incapacitated during the attack.

Treatment guide

- **Specific antimigraine**
- **antiemetics.**
- **Combination of a longer acting analgesic like naproxen with a triptan may be more suitable for patients who have prolonged migraine attacks and suffer recurrences when treated with *treiptan alone***
- **Prophylactic regimens lasting 6 months or more are recommended.**